

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT**NOTIFICATION OF ELECTION**
(PCT Rule 61.2)**Date of mailing (day/month/year)**
19 March 2001 (19.03.01)

To:
**Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE**

in its capacity as elected Office

International application No.
PCT/GB00/02430**Applicant's or agent's file reference**
PCB/P088437PWO**International filing date (day/month/year)**
06 July 2000 (06.07.00)**Priority date (day/month/year)**
08 July 1999 (08.07.99)**Applicant**

BRENCHLEY, Paul, Ernest, Charles et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

30 January 2001 (30.01.01)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

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PATENT COOPERATION TREATY

PCT

REC'D 08 OCT 2001
14

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCB/P088437PWO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/02430	International filing date (day/month/year) 06/07/2000	Priority date (day/month/year) 08/07/1999
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant THE VICTORIA UNIVERSITY OF MANCHESTER		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 30/01/2001	Date of completion of this report 02.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Knudsen, H Telephone No. +49 89 2399 8696



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02430

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-43 as originally filed

Claims, No.:

1-18 with telefax of 19/09/2001

Drawings, sheets:

1/2,2/2 as originally filed

Sequence listing part of the description, pages:

1-5, filed with the letter of 06.09.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02430

- the description, pages:
 the claims, Nos.:
 the drawings, sheets:
5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-18
	No: Claims
Inventive step (IS)	Yes: Claims 1-18
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-18
	No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02430

Re Item I

Basis of the opinion

The sequence listing pages 1-5, filed with the letter of 06.09.2000 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
Reference is made to the following document/s/:

- D1: DATABASE NCBI [Online] AC AF095785, 14 January 1999, ISAAC ET AL.: 'Two novel polymorphisms in the promoter region of the human vascular endothelial growth factor (VEGF) gene'.
- D2: HYDER SALMAN M ET AL: 'Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins.' MOLECULAR ENDOCRINOLOGY, vol. 13, no. 6, June 1999, pages 806-811, ISSN: 0888-8809
- D3: FERRARA N: 'Vascular Endothelial Growth Factor' EUROPEAN JOURNAL OF CANCER, GB, PERGAMON PRESS, OXFORD, vol. 32A, no. 14, 1996, pages 2413-2422, ISSN: 0959-8049
- D4: WILSON ANTHONY G ET AL: 'Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 7, 1997, pages 3195-3199, ISSN: 0027-8424
- D5: HUTCHINSON ET AL.: 'Consequences for acute and chronic organ allograft rejection' GRAFT, vol. 1, no. 5, 1998, pages 186-192.
- D6: PERREY ET AL.: 'Genotyping for polymorphisms in interferon-gamma, interleukin-10, transforming growth factor-beta1 and tumor necrosis factor-alpha genes: a technical report' TRANS IMMUNOL, vol. 6, 1998, page 193.

- D7: PRAVICA V ET AL: 'In vitro production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene.' EUROPEAN JOURNAL OF IMMUNOGENETICS, vol. 26, no. 1, February 1999, pages 1-3, ISSN: 0960-7420
- D8: OWENS PATRICK E ET AL: 'VEGF promoter polymorphisms and the risk of ischaemic heart disease.' JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., vol. 35, no. 2 suppl. A, February 2000, page 306A 29th Annual Scientific Session of the American College of Cardiology.;Anaheim, California, USA; March 12-15, 2000 ISSN: 0735-1097
- D9: BROGAN IAIN J ET AL: 'Novel polymorphisms in the promoter and 5' UTR regions of the human vascular endothelial growth factor gene.' HUMAN IMMUNOLOGY, vol. 60, no. 12, December 1999, pages 1245-1249, ISSN: 0198-8859

NOVELTY & INVENTIVE STEP:

5.1 D1 discloses that two polymorphisms have been identified in the VEGF. However, no work on linking these polymorphisms to diseases has been carried out. Nevertheless, D2 teaches that polymorphisms in VEGF are expected to have impact on different physiological processes (see D2, p.810, last sentence) and D3 teaches that the loss of one allele of the VEGF gene has lethal effect on fetal development.

In view of this teaching, the IPEA is of the opinion that it would be obvious to the skilled person to search for further polymorphisms in VEGF in order to link those to diseases, especially because above documents D4-D7 show that this has been done for a number of other cytokines. However, none of the cited prior art documents disclose the G → C polymorphism at positions -460 and the C → T polymorphism at +405 and given that these polymorphisms are shown in the description to be linked to certain diseases, an inventive step is acknowledged for the subject-matter of claim 1 and its dependent claims 2-18.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02430

INDUSTRIAL APPLICABILITY:

- 5.2 The claimed subject-matter concerns an in-vitro method for diagnosis and is therefore considered industrially applicable.

P-DOCUMENTS:

- 5.3 D8 and D9 are published after the present application's priority date, but before its filing date and are therefore relevant prior art to the claimed subject-matter, if any, which does not have a valid claim to priority.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5(a)(ii) PCT, the closest prior art documents D1-D3 are not identified in the description and the relevant background art disclosed therein is not briefly discussed.

Re Item VIII

Certain observations on the international application

The description does not disclose other polymorphisms at -460 and +405 than C→T and G→C, respectively. Thus, claim 1 lacks support in the description insofar as they concern other polymorphisms than those two specific polymorphisms, in particular because a specific polymorphism seem to predispose for a specific disease (see page 9 of the present application).

CLAIMS:

1. An *in vitro* method for diagnosing or detecting a predisposition to a disease or disorder associated with abnormal Vascular Endothelial Growth Factor gene expression, the method comprising examining regulatory elements associated with the Vascular Endothelial Growth Factor gene to detect the presence of a genetic polymorphism which is linked to the disease or disorder.
2. A method as claimed in claim 1 carried out on genomic DNA.
3. A method as claimed in claim 2 in which the genomic DNA is isolated from blood or tissue samples.
4. A method as claimed in any preceding claim in which a region around 405 bases 3' of the transcription start of the Vascular Endothelial Growth Factor gene is examined to detect the presence of a genetic polymorphism.
5. A method as claimed in claim 4 in which the region is examined to detect the presence of a genetic polymorphism from Guanine to Cytosine.
6. A method as claimed in any one of claims 1 to 3 in which a region around 460 bases 5' of the transcription start of the Vascular Endothelial Growth Factor gene is examined to detect the presence of a genetic polymorphism.
7. A method as claimed in claim 6 in which the region is examined to detect the presence of a genetic polymorphism from Cytosine to Thymine.

8. A method as claimed in any preceding claims wherein the presence of a genetic polymorphism is determined by amplification of at least a fragment of the DNA by polymerase chain reaction (PCR).
9. A method as claimed in claim 8 in which the DNA is subjected to PCR amplification using PCR primers specific for the region defined by claim 5.
10. A method according to claim 9 wherein the primers are:
5'ATTTATTTTGCTTGCATT3' (SEQ ID No. 1); and
5'GTCTGTCTGTCTGTCCGTCA3' (SEQ ID No. 2)
11. A method as claimed in claim 8 in which the DNA is subjected to PCR amplification using PCR primers specific for the region defined by claim 7.
11. A method according to claim 11 wherein the primers are:
5'TGTGCGTGTGGGGTTGAGCG 3' (SEQ ID No. 5); and
5'TACGTGCGGACAGGGCCTGA 3' (SEQ ID No. 4).
13. A method according to any preceding claim further comprising the step of analysing the amplification product by restriction digestion and size analysis.
14. A method according to any preceding claim wherein the disease or disorder is ischaemic heart disease.
15. A method according to any one of claims 1 – 13 wherein the disease or disorder is Nephrotic Syndrome.
16. A method according to any one of claims 1 – 13 wherein the disease or disorder is an inflammatory joint disorder.

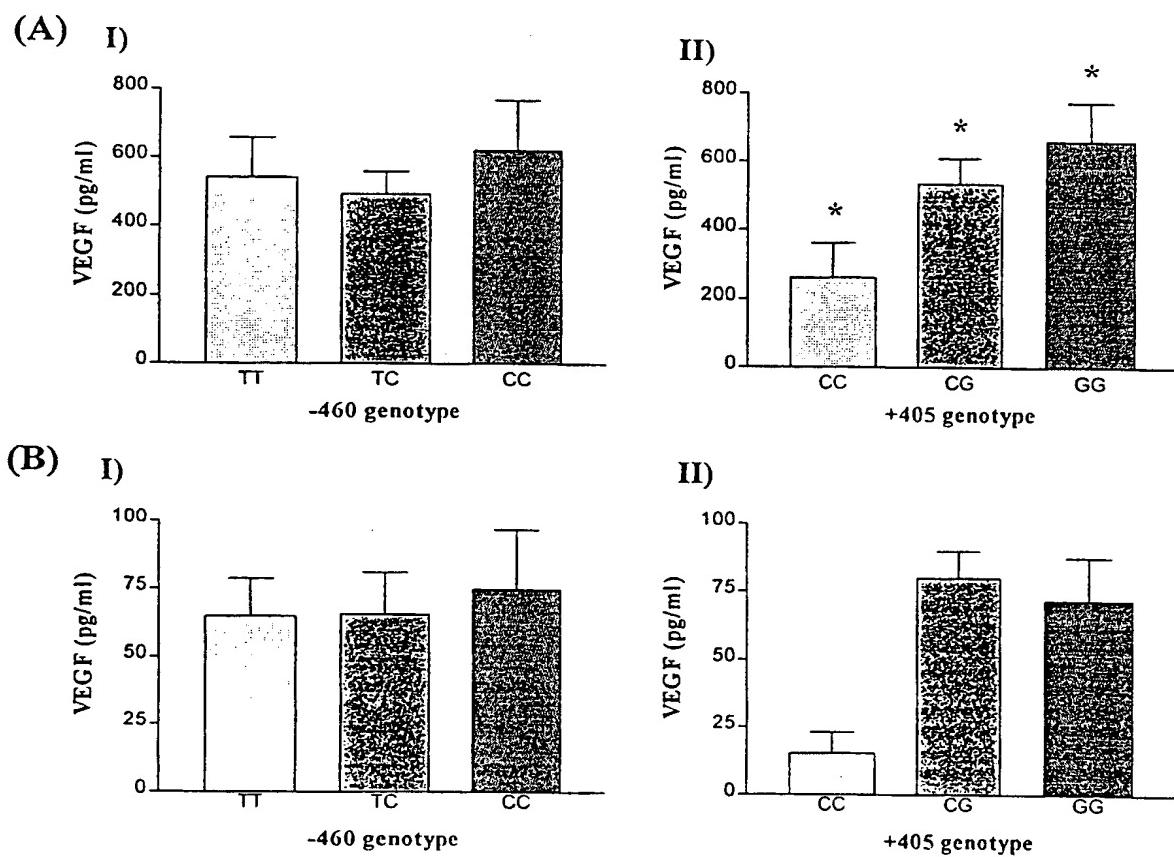
17. A method according to claim 16 wherein the disorder is Rheumatoid Arthritis.
18. A method according to any one of claims 1 – 13 wherein the disease or disorder is cancer.
19. A method according to claim 18 wherein the cancer is Ovarian Carcinoma
20. A method according to any one of claims 1 – 13 wherein the disease or disorder is diabetes, or complications thereof, or proteinuria.
21. A kit, for use in the method according to any one of claims 8 – 20, comprising:
 - A) PCR primers for amplifying genetic polymorphisms in regulatory elements associated with the Vascular Endothelial Growth Factor gene that are linked to a disease or disorder; and
 - B) Control DNA samples of known genotype for each polymorphism.
22. The Kit according to claim 21 wherein the PCR primers are as defined in claim 9.
23. The Kit according to claim 21 wherein the PCR primers are as defined in claim 11.
24. The kit according to any one of claims 21 – 23 wherein the kit further comprises a suitable restriction enzyme for generating fragments of DNA.
25. The kit according to any one of claims 21 – 24 wherein the kit further comprises a data card outlining linkage between a particular polymorphism and a disease and/or protocols for PCR amplification, restriction enzyme digestion of PCR products and agarose gel electrophoresis of DNA fragments;

26. The kit according to any one of claims 21 – 25 wherein the kit further comprises buffers for use in the method according to any one of claim 8 – 20.
27. The kit according to claim 26 wherein the kit comprises at least one of the buffers A- D from Example 4.

FIG. 1

→ transcription start

SUBSTITUTE SHEET (RULE 26)

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02430

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE NCBI 'Online! AC AF095785, 14 January 1999 (1999-01-14) ISAAC ET AL.: "Two novel polymorphisms in the promoter region of the humanvascular endothelial growth factor (VEGF) gene" XP002160600 abstract</p> <p>---</p>	1-27
Y	<p>HYDER SALMAN M ET AL: "Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins." MOLECULAR ENDOCRINOLOGY, vol. 13, no. 6, June 1999 (1999-06), pages 806-811, XP000979039 ISSN: 0888-8809 See page 810, last sentence. the whole document</p> <p>---</p> <p>-/-</p>	1-27

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

16 February 2001

Date of mailing of the international search report

01/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02430

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FERRARA N: "VASCULAR ENDOTHELIAL GROWTH FACTOR" EUROPEAN JOURNAL OF CANCER, GB, PERGAMON PRESS, OXFORD, vol. 32A, no. 14, 1996, pages 2413-2422, XP002910093 ISSN: 0959-8049 the whole document ---	1-27
A	WILSON ANTHONY G ET AL: "Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 7, 1997, pages 3195-3199, XP002160597 1997 ISSN: 0027-8424 the whole document ---	
A	HUTCHINSON ET AL.: "Consequences for acute and chronic organ allograft rejection" GRAFT, vol. 1, no. 5, 1998, pages 186-192, XP002160598 See "Variation in cytokine genes", page 187 the whole document ---	
A	PERREY ET AL.: "Genotyping for polymorphisms in interferon-gamma, interleukin-10, transforming growth factor-beta1 and tumor necrosis factor-alpha genes: a technical report" TRANS IMMUNOL, vol. 6, 1998, page 193 XP000982277 the whole document ---	
A	PRAVICA V ET AL: "In vitro production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene." EUROPEAN JOURNAL OF IMMUNOGENETICS, vol. 26, no. 1, February 1999 (1999-02), pages 1-3, XP000982120 ISSN: 0960-7420 the whole document ---	
A	DATABASE GCG_GENESEQ 'Online' ID/AC: T65724, WEBER ET AL.: "Repeat sequence from polymorphic marker clone Mfd22" XP002160601 abstract ---	
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02430

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE NCBI 'Online! AC:M63971, 3 August 1993 (1993-08-03) TISCHER ET AL.: "The human gene for vascular endothelial growth factor: Multiple protein forms are encoded through alternative exon splicing" XP002160602 abstract</p> <p>---</p>	
P,X	<p>OWENS PATRICK E ET AL: "VEGF promoter polymorphisms and the risk of ischaemic heart disease." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., vol. 35, no. 2 suppl. A, February 2000 (2000-02), page 306A XP000979065 29th Annual Scientific Session of the American College of Cardiology.; Anaheim, California, USA; March 12-15, 2000 ISSN: 0735-1097 the whole document</p> <p>---</p>	1-27
P,X	<p>BROGAN IAIN J ET AL: "Novel polymorphisms in the promoter and 5' UTR regions of the human vascular endothelial growth factor gene." HUMAN IMMUNOLOGY, vol. 60, no. 12, December 1999 (1999-12), pages 1245-1249, XP000979038 ISSN: 0198-8859</p> <p>the whole document</p> <p>---</p>	1-3,8
P,Y		4-7,9-27

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04351 A2(51) International Patent Classification⁷:**C12Q 1/68**(74) Agent: BANFORD, Paul, Clifford; Marks & Clerk,
Sussex House, 83-85 Mosley Street, Manchester M2 3LG
(GB).

(21) International Application Number: PCT/GB00/02430

(22) International Filing Date: 6 July 2000 (06.07.2000)

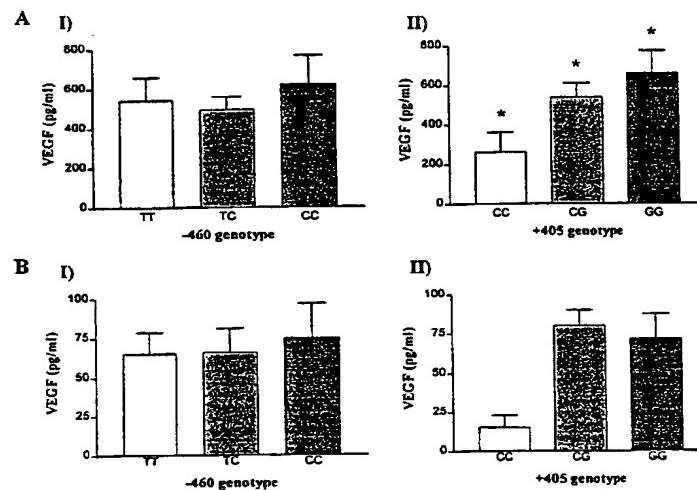
(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(30) Priority Data:
9915978.2 8 July 1999 (08.07.1999) GB
9921801.8 16 September 1999 (16.09.1999) GB(71) Applicant (*for all designated States except US*): THE
VICTORIA UNIVERSITY OF MANCHESTER
[GB/GB]; Oxford Road, Manchester M13 9PL (GB).**Published:**— *Without international search report and to be republished
upon receipt of that report.**For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: GENETIC TESTING

**WO 01/04351 A2**(57) Abstract: The present invention relates to an *in vitro* method for diagnosing or detecting a predisposition to a disease or disorder associated with abnormal Vascular Endothelial Growth Factor gene expression and kits for use in such a method. The method comprises examining regulatory elements associated with the Vascular Endothelial Growth Factor gene to detect the presence of a genetic polymorphism which is linked to the disease or disorder.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCB/P088437PWO	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB 00/02430	International filing date (<i>day/month/year</i>) 06/07/2000	(Earliest) Priority Date (<i>day/month/year</i>) 08/07/1999
Applicant THE VICTORIA UNIVERSITY OF MANCHESTER		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

GENETIC TEST FOR DETECTING A PREDISPOSITION TO A DISEASE ASSOCIATED WITH
ABNORMAL VEGF GENE EXPRESSION

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

2 _____

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02430

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE NCBI 'Online! AC AF095785, 14 January 1999 (1999-01-14) ISAAC ET AL.: "Two novel polymorphisms in the promoter region of the humanvascular endothelial growth factor (VEGF) gene" XP002160600 abstract</p> <p>---</p> <p>HYDER SALMAN M ET AL: "Regulation of angiogenic growth factors in the female reproductive tract by estrogens and progestins." MOLECULAR ENDOCRINOLOGY, vol. 13, no. 6, June 1999 (1999-06), pages 806-811, XP000979039 ISSN: 0888-8809 See page 810, last sentence. the whole document</p> <p>---</p> <p>-/-</p>	1-27
Y		1-27

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

16 February 2001

Date of mailing of the international search report

01/03/2001

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02430

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FERRARA N: "VASCULAR ENDOTHELIAL GROWTH FACTOR" EUROPEAN JOURNAL OF CANCER, GB, PERGAMON PRESS, OXFORD, vol. 32A, no. 14, 1996, pages 2413-2422, XP002910093 ISSN: 0959-8049 the whole document ---	1-27
A	WILSON ANTHONY G ET AL: "Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 94, no. 7, 1997, pages 3195-3199, XP002160597 1997 ISSN: 0027-8424 the whole document ---	
A	HUTCHINSON ET AL.: "Consequences for acute and chronic organ allograft rejection" GRAFT, vol. 1, no. 5, 1998, pages 186-192, XP002160598 See "Variation in cytokine genes", page 187 the whole document ---	
A	PERREY ET AL.: "Genotyping for polymorphisms in interferon-gamma, interleukin-10, transforming growth factor-beta1 and tumor necrosis factor-alpha genes: a technical report" TRANS IMMUNOL, vol. 6, 1998, page 193 XP000982277 the whole document ---	
A	PRAVICA V ET AL: "In vitro production of IFN-gamma correlates with CA repeat polymorphism in the human IFN-gamma gene." EUROPEAN JOURNAL OF IMMUNOGENETICS, vol. 26, no. 1, February 1999 (1999-02), pages 1-3, XP000982120 ISSN: 0960-7420 the whole document ---	
A	DATABASE GCG_GENESEQ 'Online' ID/AC: T65724, WEBER ET AL.: "Repeat sequence from polymorphic marker clone Mfd22" XP002160601 abstract ---	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	<p>DATABASE NCBI 'Online! AC:M63971, 3 August 1993 (1993-08-03) TISCHER ET AL.: "The human gene for vascular endothelial growth factor: Multiple protein forms are encoded through alternative exon splicing" XP002160602 abstract</p> <p>---</p>	
P,X	<p>OWENS PATRICK E ET AL: "VEGF promoter polymorphisms and the risk of ischaemic heart disease." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY., vol. 35, no. 2 suppl. A, February 2000 (2000-02), page 306A XP000979065 29th Annual Scientific Session of the American College of Cardiology.; Anaheim, California, USA; March 12-15, 2000 ISSN: 0735-1097 the whole document</p> <p>---</p>	1-27
P,X	<p>BROGAN IAIN J ET AL: "Novel polymorphisms in the promoter and 5' UTR regions of the human vascular endothelial growth factor gene." HUMAN IMMUNOLOGY, vol. 60, no. 12, December 1999 (1999-12), pages 1245-1249, XP000979038 ISSN: 0198-8859</p> <p>the whole document</p> <p>-----</p>	1-3,8
P,Y		4-7,9-27